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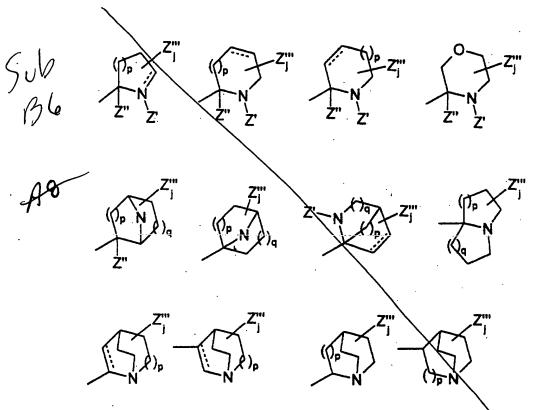
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Filed: For:

PHARMACEUTICAL COMPOSITIONS AND METHODS FOR USE



where Z' is hydrogen, lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z" is hydrogen or lower alkyl; and Z" is a non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; the dotted line indicates a carbon-carbon single bond or a carbon-carbon double bond; p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3.

73. The method of Claim 66 wherein X' is COR' where R' is selected from the (Amended) group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, non-aromatic heterocyclyl, substituted non-aromatic heterocyclyl, non-aromatic heterocyclylalkyl and substituted non-aromatic hetero-cyclylalkyl.

REMARKS

Claims 1-16, 22-41, 48-66 and 73-75 are pending. Claims 1-3, 16, 22, 25-27, 41, 48, 51-53, 66 and 73 are amended for clarity. Claims 17-21, 42-47 and 67-72 have been canceled in view of the restriction requirement. Entry of the amendments and examination on the merits are respectfully requested.

Restriction and Election of Species

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The February 13, 2002 Office Action restricted the claims to one of the following groups, and requested an election of species:

Group I:

Claim 1-75, where X' and X are both nitrogen

Group II:

Claim 1-75, where X' is nitrogen and X is carbon

Group III:

Claim 1-75, where X' is carbon and X is nitrogen

Group IV:

Claim 1-75, where X' and X are both carbon

Applicants elect Group IV without traverse, and have amended the claims accordingly. Applicants elect (S)-5-(2-pyrrolidin-2-ylethynyl)pyridine as the species.

For at least the reasons set forth herein, Applicants submit all of pending claims 1-16, 22-41, 48-66 and 73-75 are in condition for examination. Prompt consideration and action are respectfully requested.

Should the Examiner have any questions, he is invited to contact Applicants' undersigned representative at the telephone number below.

Respectfully submitted,

<u>3/13/02</u>

Registration No. 37,783

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APPENDIX - AMENDED CLAIMS

1. (Amended) A compound of the formula:

$$X = CH = CH - (CEE^{I})_{m} - (CE^{II}E^{III})_{n} - Q$$

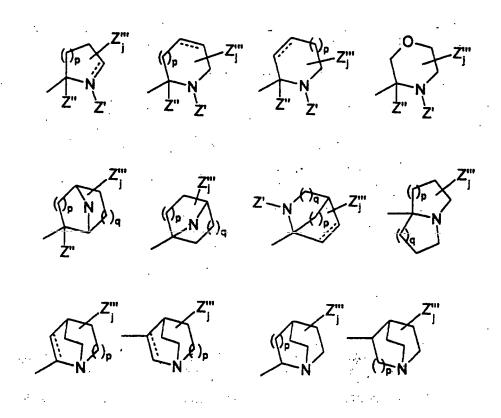
where [each of] X and X' are individually [nitrogen, nitrogen bonded to oxygen or] carbon bonded to a substituent species [characterized as having a sigma m value between about -0.3 and about 0.75] selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl; arylalkyl, substituted arylalkyl, halo, -OR', -NR'R", -CF₃, -CN, -NO₂, -C₂R', -SR', -N₃, C(=O)NR'R", -NR'C(=O)R", -C(=O)R', -C(=O)OR', --O(CR'R''), C(=O)R', -O(CR'R"),NR'R" -O(CR'R'').NR"C(=O)R', O(CR'R''), $NR''SO_2R'$, -OC(=O)NR'R'', -NR'C(=O)OR'', $-SO_2R'$, $-SO_2NR'R''$, and $-NR'SO_2R''$, where R' and R" are individually hydrogen, lower alkyl, cycloalkyl, heterocyclyl, or an aromatic group-containing species and r is an integer from 1 to 6, or R' and R" can together form a cycloalkyl functionality; m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3: E. E^I, E^{II} and E^{III} individually represent hydrogen or a suitable non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; and Q is selected from:

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where Z' represents hydrogen or lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z" is hydrogen or lower alkyl; and Z" is a non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; the dotted line indicates a carbon-carbon single bond or a carbon-carbon double bond, p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3.

- The compound of Claim 1 wherein X' is [OCx where Cx] COR' where R' 2. (Amended) is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted non-aromatic heterocyclyl, non-aromatic non-aromatic heterocyclylalkyl and substituted non-aromatic heterocyclylalkyl.
- 3. (Amended) The compound of Claim 2 wherein [Cx] R' is phenyl or substituted phenyl.
- 16. (Amended) A compound of the formula:

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$$C = C - (CEE^{I})_{m} - (CE^{I}E^{II})_{n} - Q$$

$$D_{k} X''$$

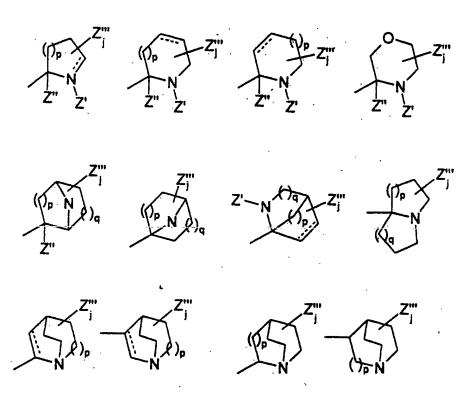
where X" is nitrogen, [each of X[,] and X' [and X"] are individually [nitrogen, nitrogen bonded to oxygen or carbon bonded to a substituent species [characterized as having a sigma m value between about -0.3 and about 0.75] selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl; arylalkyl, substituted arylalkyl, halo, -OR', -NR'R", -CF₃, -CN, -NO₂, -C₂R', -SR', -N₃, C(=O)NR'R", -NR'C(=O)R'', -C(=O)R', -C(=O)OR', -OC(=O)R', -O(CR'R''), C(=O)R', -O(CR'R''), NR'R'' $O(CR'R'')NR''C(=O)R', -O(CR'R'')NR''SO_2R', -OC(=O)NR'R'', -NR'C(=O)O R'', -SO_2R', -OC(=O)NR'R'', -SO_2R', -OC(=O)NR'R'', -SO_2R'', -$ SO₂NR'R", and -NR'SO₂R", where R' and R" are individually hydrogen, lower alkyl, cycloalkyl, heterocyclyl, or an aromatic group-containing species and r is an integer from 1 to 6, or R' and R" can together form a cycloalkyl functionality; A is O, C=O or a covalent bond; D is a suitable non-hydrogen substituent species [characterized as having a sigma m value between about -0.3 and about 0.75] selected from the group of substituent species for X, X' and X"; k is 0, 1 or 2; Cx is selected from a group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl. substituted non-aromatic heterocyclyl. non-aromatic heterocyclylalkyl and substituted non-aromatic heterocyclylalkyl; m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3; E, E^I, E^{II} and E^{III} individually represent hydrogen or a suitable non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; and Q is selected from:

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where Z' represents hydrogen or lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z" is hydrogen or lower alkyl; and Z" is a non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; the dotted line indicates a carbon-carbon single bond or a carbon-carbon double bond; p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3.

- 22. (Amended) The compound of Claim 16 wherein X' is [OCy where Cy] <u>COR' where R'</u> is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, non-aromatic heterocyclyl, substituted non-aromatic heterocyclylalkyl and substituted non-aromatic hetero-cyclylalkyl.
- 24. (Amended) The compound of claim 16 selected from the group consisting of [(S)-5-(2pyrrolidin-2-ylethynyl)pyrimidine, (R)-5-(2-pyrrolidin-2-ylethynyl)pyrimidine,] pyrrolidin-2-ylethynyl)pyridine, (R)-5-(2-pyrrolidin-2-ylethynyl)pyridine, (S)-3-isopropoxy-5-(pyrrolidin-2-ylethynyl)pyridine, (S)-3-phenyl-5-(pyrrolidin-2-ylethynyl)pyridine, (S)-3phenoxyphenyl-5-(pyrrolidin-2-ylethynyl)pyridine, (S)-3-(4-methoxyphenyl)-5-(pyrrolidin-2-(S)-3-(4-hydroxyphenyl)-5-(pyrrolidin-2-ylethynyl)pyridine, ylethynyl)pyridine, cyclopentyloxy-5-(pyrrolidin-2-ylethynyl)pyridine, (S)-3-cyclohexyloxy-5-(pyrrolidin-2ylethynyl)pyridine, (S)-3-(4-pyrrolidine-1-sulfonyl)phenoxy-5-(pyrrolidin-2-ylethynyl)pyridine, (S)-3-pyridyloxy-5-(pyrrolidin-2-ylethynyl)pyridine, (S)-3-pyrrolidin-2-ylethynyl)-5-(tetrahydropyran-4-yloxy)pyridine and (S)-3-(3,5-dihydroxy)phenoxy-5-(pyrrolidin-2ylethynyl)pyridine.

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25. (Amended) A pharmaceutical composition incorporating a compound of

$$X \longrightarrow CH = CH - (CEE^{I})_m - (CE^{II}E^{III})_n - Q$$

where each of X and X' are individually [nitrogen, nitrogen bonded to oxygen or] carbon bonded to a substituent species [characterized as having a sigma m value between about -0.3 and about 0.75] selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl; arylalkyl, substituted arylalkyl, halo, -OR', -NR'R", -CF₃, -CN, -NO₂, -C₂R', -SR', -N₃, C(=O)NR'R", -NR'C(=O)R", -C(=O)R', -C(=O)OR', -OC(=O)R'-O(CR'R''), C(=O)R', -O(CR'R"),NR'R" -O(CR'R''), NR"C(=O)R', O(CR'R"),NR"SO₂R', -OC(=O)NR'R", -NR'C(=O)O R", -SO₂R', -SO₂NR'R", and -NR'SO₂R", where R' and R" are individually hydrogen, lower alkyl, cycloalkyl, heterocyclyl, or an aromatic group-containing species and r is an integer from 1 to 6, or R' and R" can together form a cycloalkyl functionality; m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3; E, E¹, E¹¹ and E¹¹¹ individually represent hydrogen or a suitable non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; and Q is selected from:

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$$Z_{j}^{m} = Z_{j}^{m} = Z_{j$$

where Z' represents hydrogen or lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z" is hydrogen or lower alkyl; and Z" is a non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; the dotted line indicates a carbon-carbon single bond or a carbon-carbon double bond; p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3.

- 26. (Amended) The pharmaceutical composition of Claim 25 wherein X' is [OCx where Cx] <u>COR'</u> where R' is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, non-aromatic heterocyclyl, substituted non-aromatic heterocyclylalkyl and substituted non-aromatic heterocyclylalkyl.
- 27. (Amended) The pharmaceutical composition of Claim 26 wherein $[Cx] \underline{R'}$ is phenyl or substituted phenyl.
- 41. (Amended) A pharmaceutical composition incorporating a compound of the formula:

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$$Cx - A \times C \equiv C - (CEE^{i})_{m} - (CE^{i}E^{II})_{n} - Q$$

$$D_{k} \times T$$

where X" is nitrogen and [each of] X[,] and X' [and X"] are individually [nitrogen, nitrogen bonded to oxygen or carbon bonded to a substituent species [characterized as having a sigma m value between about -0.3 and about 0.75] selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl; arylalkyl, substituted arylalkyl, halo, -OR', -NR'R", -CF₃, -CN, -NO₂, -C₂R', -SR', -N₃, C(=O)NR'R", -NR'C(=O)R'', -C(=O)R', -C(=O)OR', -OC(=O)R', -O(CR'R''), C(=O)R', -O(CR'R''), NR'R'' $O(CR'R'')_{N}NR''C(=O)R', -O(CR'R'')_{N}NR''SO_{2}R', -OC(=O)NR'R'', -NR'C(=O)O R'', -SO_{2}R',$ SO₂NR'R", and -NR'SO₂R", where R' and R" are individually hydrogen, lower alkyl, cycloalkyl, heterocyclyl, or an aromatic group-containing species and r is an integer from 1 to 6, or R' and R" can together form a cycloalkyl functionality; A is O, C=O or a covalent bond; D is a suitable non-hydrogen substituent species [characterized as having a sigma m value between about -0.3 and about 0.75] selected from the group of substituent species for X, X' and X"; k is 0, 1 or 2; Cx is selected from a group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, substituted non-aromatic heterocyclyl, non-aromatic heterocyclyl, non-aromatic heterocyclylalkyl and substituted non-aromatic hetero-cyclylalkyl; m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3; E, E^I, E^{II} and E^{III} individually represent hydrogen or a suitable non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; and Q is selected from:

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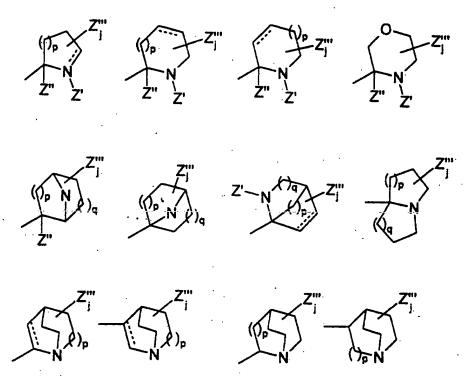
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where Z' represents hydrogen or lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z" is hydrogen or lower alkyl; arid Z" is a non-hydrogen substituent <u>selected from the group consisting of alkyl</u>, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; the dotted line indicates a carbon-carbon single bond or a carbon-carbon double bond; p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3.

- 48. (Amended) The pharmaceutical composition of Claim 41 wherein X' is [OCy where Cy] <u>COR' where R'</u> is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, non-aromatic heterocyclyl, substituted non-aromatic heterocyclylalkyl and substituted non-aromatic heterocyclylalkyl.
- 51. (Amended) A method for treating a central nervous system disorder, said method comprising administering an effective amount of a compound having the formula:

$$X = CH = CH - (CEE^{I})_{m} - (CE^{II}E^{III})_{n} - Q$$

where each of X and X' are individually [nitrogen, nitrogen bonded to oxygen or] carbon bonded to a substituent species [characterized as having a sigma m value between about -0.3 and about 0.75] selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl,



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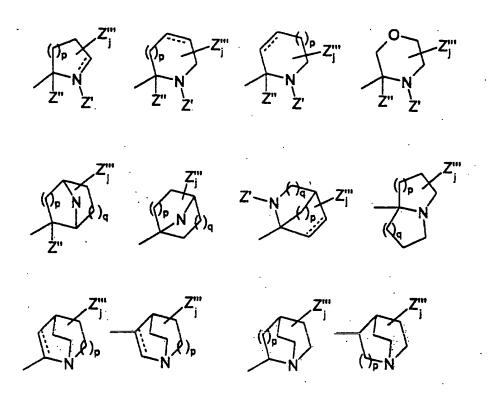
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substituted alkenyl, heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl; arylalkyl, substituted arylalkyl, halo, -OR', -NR'R", -CF₃, -CN, -NO₂, -C₂R', -SR', -N₃, C(=O)NR'R", -NR'C(=O)R", -C(=O)R', -C(=O)OR', -OC(=O)R', -O(CR'R''), C(=O)R', -O(CR'R"),NR'R" -O(CR'R''), NR''C(=O)R', O(CR'R"),NR"SO₂R', -OC(=O)NR'R", -NR'C(=O)O R", -SO₂R', -SO₂NR'R", and -NR'SO₂R", where R' and R" are individually hydrogen, lower alkyl, cycloalkyl, heterocyclyl, or an aromatic group-containing species and r is an integer from 1 to 6, or R' and R" can together form a cycloalkyl functionality; m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3; E, E^I, E^{II} and E^{III} individually represent hydrogen or a suitable non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; and Q is selected from:



where Z' [individually represent] is hydrogen, [or] lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z" is hydrogen or lower alkyl; and Z" is a non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; the dotted line indicates a carboncarbon single bond or a carbon-carbon double bond; p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3.

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52. The method of Claim 51 wherein X' is [OCx where Cx] COR' where R' is (Amended) selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl. substituted non-aromatic heterocyclyl, non-aromatic heterocyclylalkyl and substituted non-aromatic heterocyclylalkyl.

53. (Amended) The method of Claim 51 wherein [Cx] R' is phenyl or substituted phenyl.

A method for treating a central nervous system disorder, said method 66. (Amended) comprising of the administration of an effective amount of a compound having the formula:

$$Cx \xrightarrow{A} X \longrightarrow C \equiv C \longrightarrow (CEE^I)_m \longrightarrow (CE^IE^{II})_n \longrightarrow Q$$

where X" is nitrogen, [each of] X[,] and X' [and X"] are individually nitrogen, nitrogen bonded to oxygen or carbon bonded to a substituent species [characterized as having a sigma m value between about -0.3 and about 0.75] selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl; arylalkyl, substituted arylalkyl, halo, -OR', -NR'R", -CF₃, -CN, -NO₂, -C₂R', -SR', -N₃, C(=O)NR'R", -NR'C(=O)R'', -C(=O)R', -C(=O)OR', -OC(=O)R', -O(CR'R''), C(=O)R', -O(CR'R''), NR'R'' $O(CR'R'')NR''C(=O)R', -O(CR'R'')NR''SO_2R', -OC(=O)NR'R'', -NR'C(=O)O R'', -SO_2R', -OC(=O)NR'R'', -NR'C(=O)O R'', -SO_2R'', -OC(=O)NR'R'', -NR'C(=O)O R'', -SO_2R'', -OC(=O)NR'R'', -NR'C(=O)O R'', -SO_2R'', -OC(=O)NR'R'', -NR'C(=O)O R'', -SO_2R'', -OC(=O)NR'R'', -SO_2R'', -OC(=O)NR'R'', -SO_2R'', -OC(=O)NR'R'', -SO_2R'', -$ SO₂NR'R", and -NR'SO₂R", where R' and R" are individually hydrogen, lower alkyl, cycloalkyl, heterocyclyl, or an aromatic group-containing species and r is an integer from 1 to 6, or R' and R" can together form a cycloalkyl functionality; A is O, C=O or a covalent bond; D is a suitable non-hydrogen substituent species [characterized as having a sigma m value between about -0.3 and about 0.75] selected from the group of substituent species for X, X' and X"; k is 0, 1 or 2; Cx is selected from a group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, non-aromatic heterocyclyl, substituted non-aromatic heterocyclyl, non-aromatic heterocyclylalkyl and substituted non-aromatic hetero-cyclylalkyl; m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3; E, E^I, E^{II} and E^{III} individually represent hydrogen or a suitable non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; and O is selected from:

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$$Z_{j}^{m} = Z_{j}^{m} = Z_{j$$

where Z' [individually represent] is hydrogen, [or] lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z" is hydrogen or lower alkyl; and Z" is a non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; the dotted line indicates a carboncarbon single bond or a carbon-carbon double bond; p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3.

73. (Amended) The method of Claim 66 wherein X' is [OCy where Cy] COR' where R' is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted non-aromatic non-aromatic heterocyclyl, non-aromatic heterocyclylalkyl and substituted non-aromatic hetero-cyclylalkyl.